Eliminating cocamidopropyl betaine-induced allergic contact dermatitis: A new, benign-by-design zwitterionic surfactant

Allison Rush¹, Tobias Futterer¹, Timothy McCarthy¹, Neil Boaz³, Karen Meyer¹, Lynn Fowler², Michael Fevola¹, Neena K. Tierney⁴, and Joseph F. Fowler, Jr.²

¹ Johnson & Johnson Consumer Inc., Skillman, NJ
² Dermatology Specialists Research, Louisville, KY
³ Eastman Chemical Company, Kingsport, TN
⁴ Neostrata Company, Inc., a Johnson & Johnson Company, Princeton, NJ

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Background & objectives

Allergic contact dermatitis (ACD)

- ACD is an inflammatory skin disease resulting from an immunogenic response to chemical sensitizers
- Incidence of cosmetic-induced ACD has increased 62% in 25 years from 16% to 25% (n = 14,911)\(^1\)

Cocamidopropyl betaine (CAPB) voted 2004 Allergen of the Year by the American Contact Dermatitis Society\(^2\)

- CAPB is a critical ingredient in most personal cleansers, making it the predominant zwitterionic surfactant used in the skin care industry (> 80% of liquid cleansers contain CAPB\(^3\)); according to Cosmetic Ingredient Review, high quality (low impurities) CAPB is considered safe as used\(^4\)
- Prevalence of ACD to CAPB is 2-10% globally\(^5\)-\(^14\)
- Many researchers attribute CAPB-induced ACD to the residual concentrations of amidoamine (AA ~ 0.3 – 3%) and dimethylaminopropylamine (DMAPA ~ 3 ppm) impurities\(^9\),\(^11\)-\(^12\)
- Development of improved zwitterionic surfactants as CAPB alternatives presents an opportunity to eliminate potential sensitizers, such as DMAPA and AA, thus reducing the risk of ACD from personal care products

Objectives

1. Develop a new zwitterionic surfactant, Cocobutyramido Hydroxysultaine (CBAHS), using novel chemistry to eliminate DMAPA and AA as allergenic impurities
2. Demonstrate hypoallergenicity of CBAHS via in vitro assays, human repeat insult patch testing, and a clinical tolerance study in a sensitive subject population with reconfirmed ACD to CAPB, AA, and/or DMAPA

References:
Vigilant molecular design of CBAHS to avoid CAPB antigens

In vitro SenCeeTox® assay revealed a significantly lower sensitization potential for CBAHS chemical components vs. CAPB

**SenCeeTox® Endpoints***

- Direct protein reactivity (glutathione depletion)
- Induction of 11 genes associated with dermal sensitization (Nrf2/Keap1/ARE signaling pathway) using a reconstructed human epidermis model (EpiDerm™)**
- Proprietary model predictions of sensitization potency (LLNA EC3 value)

* SenCeeTox® is trademark of the testing facility: Cyprotex US, an Evotec Company
** EpiDerm™ is trademark of MatTek Corporation

Human repeat insult patch testing (n = 218) confirmed that CBAHS is hypoallergenic
Clinical assessment of CBAHS tolerance in CAPB-sensitive subjects

Overall objective: Evaluate the allergenicity potential of CBAHS among subjects with reconfirmed ACD to CAPB, AA, and/or DMAPA as determined by epicutaneous patch testing.*

Clinical study design:

Screening criteria

• Clinically-determined history of ACD to CAPB, AA, and/or DMAPA

Phase 1: Epicutaneous patch testing

• Confirm ACD to CAPB, AA, and/or DMAPA
• Confirm no predisposition to CBAHS-induced ACD

Phase 2: In-use study

• Evaluate the tolerance of a CBAHS (4.4%) test cleanser over 4 weeks of use

Key success criteria: Tolerance of a CBAHS test cleanser during a four-week controlled in-use study

Primary outcome measure: Cumulative contact dermatitis score normalized to the body surface area (BSA) affected and categorized according to best diagnosis

Contact dermatitis scores

Visible rash/redness

Itching/burning/stinging

Dryness/tightness

Best diagnosis

Allergic contact dermatitis (ACD)

Irritant contact dermatitis (ICD)

Both

Uncertain

Body surface area (BSA) affected

Per body region

Adjusted according to the “Rule of nines”

Cumulative BSA adjusted score per best diagnosis

Range = 0 – 3

Range = 0 – 9

* Note: subjects were recruited from Dr. Fowler’s patient database (Louisville, KY)

Presented at the American Academy of Dermatology Annual Meeting, 16-20 February 2018, San Diego, California, USA
Clinical results & conclusions

Epicutaneous patch test results (n = 16)

ACD to CAPB, AA, and/or DMAPA was reconfirmed in 13 out of 16 subjects
  - Ranking of ACD prevalence and severity: DMAPA > AA > CAPB

No predisposition to CBAHS-induced ACD
  - 1 subject exhibited a positive allergic reaction to the CBAHS negative control (0.5% sodium benzoate), thus all CBAHS concentrations = false positive for CBAHS

CBAHS showed exemplary tolerance in CAPB-sensitive subjects

** Zero incidence of CBAHS-induced ACD or ICD in subjects with reconfirmed ACD to CAPB, AA, and/or DMAPA
- Highest observed ACD score = 0.040 (0.44% of maximum BSA adjusted score) from a poison ivy exposure
- Isolated on posterior arms at Week 1
- Reported as an adverse event with doubtful relation to CBAHS cleanser
- Etiology = licking lips or scratching eyes

** Highest observed ICD score = 0.013 (0.14% of maximum BSA adjusted score) from chronic irritation

Four-week in-use study results (n = 11)

- Significant improvements were observed in clinical assessments at Weeks 1 and 4 vs. baseline for non-ACD/ICD related (uncertain diagnosis) dryness/tightness and BSA affected by skin irritation
- Significant improvements were observed in self-perceived attributes associated with dermatitis including dryness, tightness, irritation/discomfort, and overall skin feel

Conclusions

Cocobutyramido Hydroxysultaine (CBAHS) is a desirable alternative to CAPB for use in personal care products to avoid the allergens intrinsic to CAPB and thus avert ACD potential

Application of holistic design thinking and green chemistry principles during CBAHS development enabled other key success criteria to be met
  - CBAHS is a naturally derived ingredient manufactured under more sustainable conditions
  - Higher foaming power to cue effective cleansing without compromising mildness

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